

CLAIMS

Please amend the presently pending claims as follows:

1. **(Currently Amended)** A method of selectively inhibiting expression of a mutant target allele of a SOD1 gene in a cell or organism comprising wild-type and mutant alleles of the gene, wherein the target allele comprises a dominant gain of function mutation that is correlated with amyotrophic lateral sclerosis, the method comprising administering to the cell or organism an siRNA that is matched completely with a mRNA sequence encoded by the mutant allele but comprises a nucleotide mismatch with a mRNA sequence encoded by the wild-type allele, specific for the target allele such that allele specific RNA interference of the mutant target allele occurs and wherein the siRNA is capable of single nucleotide discrimination such that expression of the mutant target allele is inhibited by at least 50% and expression of the wild-type allele is not inhibited preserved.

2-4. **(Cancelled)**

5. **(Previously Presented)** The method of claim 1, wherein the siRNA is targeted to the gain of function mutation.

6. **(Cancel)**

7. **(Previously Presented)** The method of claim 1, wherein the mutant and wild-type alleles differ by only one, two, or three nucleotides.

8. **(Previously Presented)** The method of claim 1, wherein the mutant and wild-type alleles differ by only a single nucleotide.

9. **(Currently Amended)** A method of selectively inhibiting expression of a mutant target allele of a SOD1 gene in a cell or organism comprising wild-type and mutant alleles of the gene, wherein the mutant target allele comprises a point mutation correlated with amyotrophic lateral sclerosis, the method comprising administering to the cell or organism

an siRNA targeted to the point mutation that is matched completely with a mRNA sequence encoded by the mutant target allele but comprises a nucleotide mismatch with a mRNA sequence encoded by the wild-type allele, such that allele specific RNA interference of the mutant target allele occurs and wherein the siRNA is capable of single nucleotide discrimination such that expression of the mutant target allele is inhibited by at least 50% and expression of the wild-type allele is not inhibited preserved.

10. **(Cancelled)**

11. **(Cancel)**

12. **(Previously Presented)** The method of claim 9, wherein the mutant and wild-type alleles differ by one, two, or three nucleotides.

13-27. **(Cancelled)**

28. **(Previously Presented)** The method of claim 9, wherein the mutant and wild-type alleles differ by a single nucleotide.

29. **(Cancel)**

30. **(Currently Amended)** The method of claim 1 or 9~~29~~, wherein the mismatch is a purine:purine mismatch.

31. **(Previously Presented)** The method of claim 30, wherein the mismatch is a G:G mismatch.

32. **(Currently Amended)** The method of claim 1 or 9~~29~~, wherein the single nucleotide mismatch is located at nucleotide position 10 (P10) relative to the 5' end of the antisense strand of the siRNA.

33. (Currently Amended) The method of claim 1 or 9 ~~29~~, wherein the ~~single~~ nucleotide mismatch is located at nucleotide position 9 (P9) relative to the 5' end of the antisense strand of the siRNA.

34-36. (Cancelled)

37. The method of claim 9, wherein the mutant allele encodes a glycine to arginine mutation at amino acid position 85 (G85R) of a SOD1 protein.

38. (Previously Presented) The method of claim 9, wherein the mutant allele encodes a glycine to alanine mutation at amino acid position 93 (G93A) of a SOD1 protein.

39. (Previously Presented) The method of claim 9, wherein the siRNA comprises (i) a sense strand sequence corresponding to the sequence set forth as SEQ ID NO: 3; and (ii) an anti-sense strand sequence set forth as SEQ ID NO: 4.

40. (Previously Presented) The method of claim 9, wherein the siRNA comprises (i) a sense strand sequence set forth as SEQ ID NO: 1; and (ii) an anti-sense strand sequence set forth as SEQ ID NO: 2.

41. (Previously Presented) The method of claim 1 or 9, wherein the siRNA is administered to cell in the form of a shRNA, wherein the shRNA is cleaved in the cell to generate the siRNA.

42. (Cancel)

43. (Currently Amended) The method of claim 41~~42~~, wherein the ~~single~~-nucleotide mismatch is located at position (P10) relative to the 5' end of the shRNA.

44. (Cancelled)

45. (Previously Presented) The method of claim 43, wherein the shRNA is a G93A SOD1 shRNA.

46. (Previously Presented) The method of claim 45, wherein the G93A SOD1 shRNA has the sequence set forth as SEQ ID NO: 16.

47. (Previously Presented) The method of claim 41, wherein the shRNA is expressed from an expression construct.

48. (Previously Presented) The method of claim 47, wherein the shRNA is expressed under the control of a RNA polymerase III (U6) promoter.